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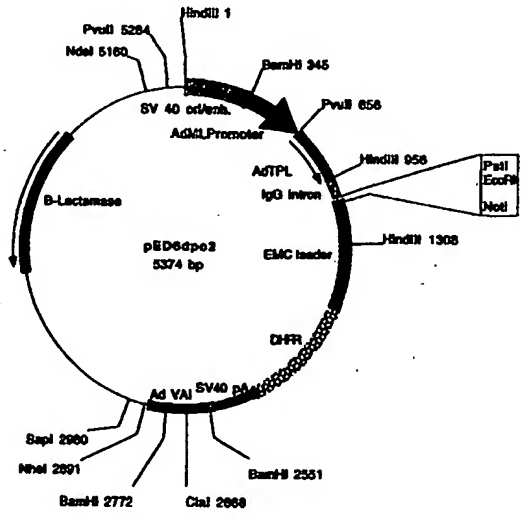
(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract

Novel polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of Ser. No. 06/XXX,XXX (converted to a provisional application from non-provisional application Ser. No. 08/780,890), filed January 9, 1997, which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 61 to nucleotide 642;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 89 to nucleotide 440;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 61 to nucleotide 642; the nucleotide sequence of SEQ ID NO:1 from nucleotide 89 to nucleotide 440; the nucleotide sequence of the full-length protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone BI164_1 deposited

under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 23 to amino acid 127.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 23 to amino acid 127;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 23 to amino acid 127.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1625 to nucleotide 1750;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1484 to nucleotide 1729;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 1625 to nucleotide 1750; the nucleotide sequence of SEQ ID NO:3 from nucleotide 1484 to nucleotide 1729; the nucleotide sequence of the full-length protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 35.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 35;

(c) fragments of the amino acid sequence of SEQ ID NO:4; and

(d) the amino acid sequence encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 35.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 99 to nucleotide 1058;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 644;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 99 to nucleotide 1058; the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 644; the nucleotide sequence of the full-length protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 182.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 182;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 182.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 237 to nucleotide 1184;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 207 to nucleotide 935;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 237 to nucleotide 1184; the nucleotide sequence of SEQ ID NO:7 from nucleotide 207 to nucleotide 935; the nucleotide sequence of the full-length protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 233.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 233;

(c) fragments of the amino acid sequence of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8 or the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 233.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 142 to nucleotide 828;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 522;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:9 from nucleotide 142 to nucleotide 828; the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 522; the nucleotide sequence of the full-length protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 127.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:9.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 127;

(c) fragments of the amino acid sequence of SEQ ID NO:10; and

(d) the amino acid sequence encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:10 or the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 127.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 3 to nucleotide 1937;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 204 to nucleotide 414;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:11 from nucleotide 3 to nucleotide 1937; the nucleotide sequence of SEQ ID NO:11 from nucleotide 204 to nucleotide 414; the nucleotide sequence of the full-length protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290. In yet other preferred

embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12 from amino acid 67 to amino acid 137.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:11.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) the amino acid sequence of SEQ ID NO:12 from amino acid 67 to amino acid 137;

(c) fragments of the amino acid sequence of SEQ ID NO:12; and

(d) the amino acid sequence encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:12 or the amino acid sequence of SEQ ID NO:12 from amino acid 67 to amino acid 137.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 137 to nucleotide 457;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 323 to nucleotide 457;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 82 to nucleotide 322;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 137 to nucleotide 457; the nucleotide sequence of SEQ ID NO:13 from nucleotide 323 to nucleotide 457; the nucleotide sequence of SEQ ID NO:13 from nucleotide 82 to nucleotide 322; the nucleotide sequence of the full-length protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 62.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 62;

(c) fragments of the amino acid sequence of SEQ ID NO:14; and

(d) the amino acid sequence encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14 or the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 62.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 312 to nucleotide 851;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 56 to nucleotide 470;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 312 to nucleotide 851; the nucleotide sequence of SEQ ID NO:15 from nucleotide 56 to nucleotide 470; the nucleotide sequence of the full-length protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 53.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 53;

(c) fragments of the amino acid sequence of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 53.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 20 to nucleotide 541;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 272 to nucleotide 541;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 448;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 20 to nucleotide 541; the nucleotide sequence of SEQ ID NO:17 from nucleotide 272 to nucleotide 541; the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 448; the nucleotide sequence of the full-length protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290; or the nucleotide sequence of the mature protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein

comprising the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 143.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 143;

(c) fragments of the amino acid sequence of SEQ ID NO:18; and

(d) the amino acid sequence encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18 or the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 143.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically

effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "BI164_1"

A polynucleotide of the present invention has been identified as clone "BI164_1". BI164_1 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BI164_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BI164_1 protein").

The nucleotide sequence of BI164_1 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BI164_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BI164_1 should be approximately 800 bp.

The nucleotide sequence disclosed herein for BI164_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BI164_1 demonstrated at least some similarity with sequences identified as AA169106 (ms65e05.r1 Stratagene mouse embryonic carcinoma (#937317) Mus musculus cDNA clone 616448 5'), AA568401 (nf16b11.s1 NCI_CGAP_Pr1 Homo sapiens cDNA clone IMAGE:913917 similar to contains element TAR1 repetitive element), and AA579465 (nf29h01.s1 NCI_CGAP_Pr1 Homo sapiens cDNA clone IMAGE:915217). Based upon sequence similarity, BI164_1 proteins and each similar protein or peptide may share at least some activity.

Clone "BK445_1"

A polynucleotide of the present invention has been identified as clone "BK445_1". BK445_1 was isolated from a human adult retina cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BK445_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BK445_1 protein").

The nucleotide sequence of BK445_1 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BK445_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BK445_1 should be approximately 3400 bp.

The nucleotide sequence disclosed herein for BK445_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BK445_1 demonstrated at least some similarity with sequences identified as F08866 (H. sapiens partial cDNA sequence; clone c-2th07), M87889 (Human

carcinoma cell-derived Alu RNA transcript, clone CD140), U52111 (Human Xq28 genomic DNA in the region of the ALD locus containing the genes for creatine transporter (SLC6A8), CDM, adrenoleukodystrophy (ALD), Na+-isocitrate dehydrogenase gamma), and Z69649 (Human DNA sequence from cosmid L69F7B, Huntington's Disease Region, chromosome 4p16.3 contains Huntington Disease (HD) gene). The predicted amino acid sequence disclosed herein for BK445_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BK445_1 protein demonstrated at least some similarity to sequences identified as L24521 (transformation-related protein [Homo sapiens]) and U22376 (alternatively spliced product using exon 13A [Homo sapiens]). Based upon sequence similarity, BK445_1 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of BK445_1 indicates that it may contain an Alu repetitive element.

Clone "BP101_2"

A polynucleotide of the present invention has been identified as clone "BP101_2". BP101_2 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. BP101_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BP101_2 protein").

The nucleotide sequence of BP101_2 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BP101_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6. Another possible reading frame and predicted amino acid sequence encoded by BP101_2 is encoded by nucleotides 992-1912 of SEQ ID NO:5 and is reported in SEQ ID NO:28; this alternative open reading frame could be joined to the reading frame reported in SEQ ID NO:6 if an insertion or deletion resulting in a frameshift was made in the sequence of SEQ ID NO:5. Amino acids 126 to 138 of SEQ ID NO:28 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 139 of SEQ ID NO:28, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BP101_2 should be approximately 2280 bp.

The nucleotide sequence disclosed herein for BP101_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BP101_2 demonstrated at least some similarity with sequences identified as M87918 (Human carcinoma cell-derived Alu RNA transcript, clone NE51), N74481 (za54d08.s1 Homo sapiens cDNA clone 296367 3' similar to contains Alu repetitive element), and W03189 (za54d08.r1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone 296367 5'). The predicted amino acid sequence disclosed herein for BP101_2 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted BP101_2 protein demonstrated at least some similarity to sequences identified as L11672 (zinc finger protein [Homo sapiens]). Based upon sequence similarity, BP101_2 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of BP101_2 indicates that it may contain an Alu repetitive element.

Clone "CD124_3"

A polynucleotide of the present invention has been identified as clone "CD124_3". CD124_3 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CD124_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CD124_3 protein").

The nucleotide sequence of CD124_3 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CD124_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CD124_3 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for CD124_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CD124_3 demonstrated at least some similarity with sequences identified as AA123334 (mq10f01.r1 Barstead MPLRB1 Mus musculus cDNA clone 578329 5'), AA215297 (zr94b03.r1 NCI_CGAP_GCB1 Homo sapiens cDNA clone), AA361664 (EST71136 T-cell lymphoma Homo sapiens cDNA 5' end), M16362 (Mouse opa repeat

mRNA, 3' end (MOUSE)), N56580 (SH2201F Homo sapiens cDNA clone), Q12515 (CSP-2 peptide from P. falciparum (clone 4)), W53105 (md14d02.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA clone 368355 5'), and X78609 (G.gallus genomic DNA repeat region, clone 16E1). Based upon sequence similarity, CD124_3 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of CD124_3 indicates that it may contain a simple repeat sequence and a chicken genomic repeat sequence.

Clone "CW924_1"

A polynucleotide of the present invention has been identified as clone "CW924_1". CW924_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CW924_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CW924_1 protein").

The nucleotide sequence of CW924_1 as presently determined is reported in SEQ ID NO:9. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CW924_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:10.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CW924_1 should be approximately 2300 bp.

The nucleotide sequence disclosed herein for CW924_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CW924_1 demonstrated at least some similarity with sequences identified as H86434 (ys93h08.r1 Homo sapiens cDNA clone 222399 5'), T15605 (IB1619 Infant brain, Bento Soares Homo sapiens cDNA 3'end similar to IB570 H. sapiens brain cDNA clone IB570), U17259 (Mus musculus p19 mRNA, complete cds (MOUSE)), and W54334 (md05b08.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA clone 367479 5'). The predicted amino acid sequence disclosed herein for CW924_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CW924_1 protein demonstrated at least some similarity to sequences identified as P50649 (Sequence encoded by brain specific (Class III) clone p1A75 ORF 1) and U17259 (p19 [Mus musculus]). The predicted CW924_1 protein

also demonstrated at least some similarity to mouse p21 protein. Based upon sequence similarity, CW924_1 proteins and each similar protein or peptide may share at least some activity. Amino acids 74 to 86 of SEQ ID NO:10 are a possible leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 87, or are a transmembrane domain.

Clone "DF518_3"

A polynucleotide of the present invention has been identified as clone "DF518_3". DF518_3 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DF518_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "DF518_3 protein").

The nucleotide sequence of DF518_3 as presently determined is reported in SEQ ID NO:11. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DF518_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:12.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DF518_3 should be approximately 2650 bp.

The nucleotide sequence disclosed herein for DF518_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DF518_3 demonstrated at least some similarity with sequences identified as AA190696 (zp89a02.r1 Stratagene HeLa cell s3 937216 Homo sapiens cDNA clone 627338 5'), H13983 (EST00009 Homo sapiens genomic clone C1-14 5'), and T90095 (yd39d08.s1 Homo sapiens cDNA clone 110607 3'). Based upon sequence similarity, DF518_3 proteins and each similar protein or peptide may share at least some activity.

Clone "DM406_1"

A polynucleotide of the present invention has been identified as clone "DM406_1". DM406_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DM406_1 is a full-length

clone, including the entire coding sequence of a secreted protein (also referred to herein as "DM406_1 protein").

The nucleotide sequence of DM406_1 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DM406_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14. Amino acids 50 to 62 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 63, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DM406_1 should be approximately 1700 bp.

The nucleotide sequence disclosed herein for DM406_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DM406_1 demonstrated at least some similarity with sequences identified as D82016 (Human fetal brain cDNA 5'-end GEN-430G10) and H12174 (ym17f08.r1 Homo sapiens cDNA clone 48073 5'). Based upon sequence similarity, DM406_1 proteins and each similar protein or peptide may share at least some activity.

Clone "EH189_1"

A polynucleotide of the present invention has been identified as clone "EH189_1". EH189_1 was isolated from a human adult blood (peripheral blood mononuclear cells treated *in vivo* with granulocyte-colony stimulating factor) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. EH189_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "EH189_1 protein").

The nucleotide sequence of EH189_1 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the EH189_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone EH189_1 should be approximately 1450 bp.

The nucleotide sequence disclosed herein for EH189_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and

FASTA search protocols. EH189_1 demonstrated at least some similarity with sequences identified as AA681168 (vr75f04.s1 Knowles Solter mouse 2 cell Mus musculus cDNA clone 1134559 5'). Based upon sequence similarity, EH189_1 proteins and each similar protein or peptide may share at least some activity.

Clone "EH203_2"

A polynucleotide of the present invention has been identified as clone "EH203_2". EH203_2 was isolated from a human adult blood (peripheral blood mononuclear cells treated *in vivo* with granulocyte-colony stimulating factor) cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. EH203_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "EH203_2 protein").

The nucleotide sequence of EH203_2 as presently determined is reported in SEQ ID NO:17. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the EH203_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18. Amino acids 1 to 84 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 85, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone EH203_2 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for EH203_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. EH203_2 demonstrated at least some similarity with sequences identified as AA482321 (ab15c05.r1 Stratagene lung (#937210) Homo sapiens cDNA clone 840872 5'), H56345 (yq97b12.s1 Homo sapiens cDNA clone 203711 3'), T92363 (ye19h06.s1 Homo sapiens cDNA clone 118235 3'). Based upon sequence similarity, EH203_2 proteins and each similar protein or peptide may share at least some activity.

Deposit of Clones

Clones BI164_1, BK445_1, BP101_2, CD124_3, CW924_1, DF518_3, DM406_1, EH189_1, and EH203_2 were deposited on January 8, 1997 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the

accession number ATCC 98290, from which each clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* **19**: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* **9**: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
BI164_1	SEQ ID NO:19
BK445_1	SEQ ID NO:20
BP101_2	SEQ ID NO:21
CD124_3	SEQ ID NO:22
CW924_1	SEQ ID NO:23
DF518_3	SEQ ID NO:24

DM406_1	SEQ ID NO:25
EH189_1	SEQ ID NO:26
EH203_2	SEQ ID NO:27

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* 15(7): 250-254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* 62(1): 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* 58: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* 14(9): 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90(16): 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91(2): 719-722; all of which are incorporated by reference herein), or through homologous recombination,

preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* 336: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides .

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

†: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

*T_B - T_R: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, T_m(°C) = 2(# of A + T bases) + 4(# of G + C bases). For hybrids between 18 and 49 base pairs in length, T_m(°C) = 81.5 + 16.6($\log_{10}$[Na^+]) + 0.41(%G+C) - (600/N), where N is the number of bases in the hybrid, and [Na^+] is the concentration of sodium ions in the hybridization buffer ([Na^+] for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium*, or any bacterial

strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant

methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art (see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which

the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays

for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for

example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or

tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science 257:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of

viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface.

Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro* antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter

7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent

myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland,

H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of

congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and

Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the

first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used

to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms; effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic

lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be

administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous, subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred

pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal

antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-

aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in

the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth
McCoy, John M.
LaVallie, Edward R.
Racie, Lisa A.
Merberg, David
Treacy, Maurice
Spaulding, Vikki
Agostino, Michael J.

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(iii) NUMBER OF SEQUENCES: 28

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(A) ADDRESSEE: Genetics Institute, Inc.
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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
(B) FILING DATE:
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Sprunger, Suzanne A.
(B) REGISTRATION NUMBER: 41,323

(ix) TELECOMMUNICATION INFORMATION:
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(B) TELEFAX: (617) 876-5851

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 719 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GCTGTTTGTA TTTTGGCTGC TGCAGGAGCC ATTTTAGAAA TAAATATCTT CCTTCAATAG 60

ATGAAAATGA AAATACAGAA AAAAGAGAAG CAGTTGTCAA ATTTAAAAGT TTTGAATCAC 120

TCCCCAATGT CTGATGCCTC TGTCAATTTT GACTACAAAT CTCCATCCCC ATTTGACTGC 180

AGCACTGATC AAGAAGAGAA AATTGAAGAT GTTGCTAGTC ACTGTCTGCC TCAGAAGGAC 240

CTGTATACTG CTGAAGAGGA AGCTGCTACC CTTTTTCCTA GGAAAATGAC ATCCCATAAT 300

GGGATGGAGG ACAGTGGAGG AGGAGGTACT GGAGTGAAGA AGAAACGGAA GAAAAAGGAG 360

CCAGGAGACC AAGAGGGTGC AGCAAAGGGA AGCAAGGACA GAGAGCCCAA GCCAAAGAGG 420

AAACGAGAAC CGAAAGAGCC AAAGGAACCC AGAAAGGCCA AGGAGCCGAA GAAGGCCAAG 480

GAGCACAAGG AGCCGAAGCA AAAAGATGGG GCAAAGAAGG CACGGAAGCC CCGGGAGGCC 540

TCGGGCACCA AGGAGGCCAA AGAGAAGAGG AGCTGCACTG ACTCTGCAGC CAGGACGAAG 600

TCCAGGAAGG CCAGCAAGGA GCAAGGACCA ACCCCAGTGG AAAAAAAAAA AAAAAAAAAA 660

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAA 719

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 194 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Lys Met Lys Ile Gln Lys Lys Glu Lys Gln Leu Ser Asn Leu Lys
1 5 10 15

Val Leu Asn His Ser Pro Met Ser Asp Ala Ser Val Asn Phe Asp Tyr
20 25 30

Lys Ser Pro Ser Pro Phe Asp Cys Ser Thr Asp Gln Glu Glu Lys Ile
35 40 45

Glu Asp Val Ala Ser His Cys Leu Pro Gln Lys Asp Leu Tyr Thr Ala
50 55 60

Glu Glu Glu Ala Ala Thr Leu Phe Pro Arg Lys Met Thr Ser His Asn
65 70 75 80

Gly Met Glu Asp Ser Gly Gly Gly Gly Thr Gly Val Lys Lys Lys Arg
85 90 95

Lys Lys Lys Glu Pro Gly Asp Gln Glu Gly Ala Ala Lys Gly Ser Lys
100 105 110

Asp Arg Glu Pro Lys Pro Lys Arg Lys Arg Glu Pro Lys Glu Pro Lys
115 120 125

Glu Pro Arg Lys Ala Lys Glu Pro Lys Lys Ala Lys Glu His Lys Glu
130 135 140

Pro Lys Gln Lys Asp Gly Ala Lys Lys Ala Arg Lys Pro Arg Glu Ala
145 150 155 160

Ser Gly Thr Lys Glu Ala Lys Glu Lys Arg Ser Cys Thr Asp Ser Ala
165 170 175

Ala Arg Thr Lys Ser Arg Lys Ala Ser Lys Glu Gln Gly Pro Thr Pro
180 185 190

Val Glu

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2584 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

AGTGATTCTC CTGCCTCAGC CTCCCGAGTA GGTGGGATTA TAGGCATGTG CCACTGTGCC 60

CGGTTTATTT TTGTATTTTT AATAGAAATG GGGTTTCACC AGGCTGGTCT TGAACTCCTG 120

ACCTCAAGTG ATCCACCCGC CTCAGCCTCT CAAGGGACTA GGATTACAGG CAAGAGCCAC 180

TGCGCCTGGC CTCTTTTAAC CATTTTGAAT TGACTTTTGT GGATGGGGTA AGATAAGGGT 240

CCAATTTCAT TTCTTGGCAT GTGGTTATCT AGCTTTTTCA ACACCATTTA TTAAAGAGAC 300

TATCCTTTCT TTATTGTGTA CTTTTGACAC CTTTGTTGAT GATTAGTTGG CCACATAAAC 360

GAGGATTTAT TTCTGGGATT CCTATTCTGT TCCATTGGTC TATATGTCTC CTTTTATGCC 420

AGTACCATAC AGTTTTGATT ACTGTAGGTC TGTAATATAA TTTGAAATGA AGTGTGATGC 480

CACCAGCTTT GTTCTTCTTG CTCAGGATCA TTTTAGATAT TCTGGGTCTT TTGGGTTCTG 540

TATGGATGTT AGGAATTTTT TTTTTTTTTC TGTGAAAAAT GTCATTGGAG TTTTGCTAGA 600

GATTGCGTTG AATCTGTAGA CTACTTTGTG TATTGCAGAC ATTTTGACAA TAATGATTCT 660

TCTGATCCTG AACATGGGAT AGCTTTCCAT TTATTTGTGT CATCTCCAGT TCTTTCATAT 720

ATGTATTATA GCTTTTTAGCA TACACATCTT TCCCCTCCTT GGTAAAACTT ATTCCTAAGT 780

ATTTTATTCC TTTTGATGCT ATTGTAAATG GGATTGCTTT CTTAATTTCT TTCTTGGATA 840

CTTCACTGTT AGTGAAGTGT AATTGATTTT TGTATGTTGA TTTTGTATCC TGAAACTTTA 900

CTGGATTCGT TTATTCATTC TAACAGTTTT TAGTGGCATA TTTAGGGTTT TCTGTATATA 960

GGATGATGTC ACCTGCAGAG ACAATTTTAC TTCTTCCTTT CTGATTTGGA TGCCTTTTAT 1020

TTCTTTTCCT TGCCTAATTT CTGTGGCTAG GATTTCTAGT ACTATGTTGA ATGTAAGTGA 1080

TAAGTGTGGG CATCCTTGTC TGTCCTTGTC ACATTCAGTT GTATGTGCAA TACTGGAACC 1140

ATCCAGCTCA TAGTCACGTA ATTCCTCTTT GTGCAGCCTC ATGTAAAATC ACACCCCTAT 1200

TCACATTTTT TTCTGTCTGT CTCCCACCTC TCCAGGTCCC TGCCCTGCAA CTTTCAGTTA 1260

CTTCAGACTC TCAGAAGACT AGCCTCTAAA TACCTCAATT TATCTGCACT ACTGTGGTCT 1320

ACTTGAAATT CTCTTCCCTC TTCTGCAGTT TGTAATGGCA TTCAGGCCAA AAACTGTAGT 1380

AGTTTTAGGG CTCTCTTCAT TTGCTTCTCT GCTCCTAGGG ATCATAGTGC TGTGCTATCT 1440

GTTGTCCAGC ATCTGACACA GTTGGTTTTA TATTTTGTCT GGTTTTCTAG TTATTAAGCA 1500

GGTTAAGTCT GGTTCCTGCT GTTCTATATA GCAGGAAGCA AAGGTTCTCT CATGAATTTT 1560

TAGCATAATA ACATAAGCGT GGATTCCAAA AATTCATTAC ACAGATCCTG GAAATCTGTT 1620

TACTATGTTT TATACATTCT GTGAAAGCTG GAGAATATAT ATTTGTTTTA CTATGTGTAT 1680

CGCAAATAAA ATATCAATTT CATGTGCCAG AGAATTGAAT ACATTATCAA AGGGTCATTT 1740

CATAACGTTA TAATCACCAT CCATCCTGTA AGTCCTTTGA AATTTCTTCT TTTCTATGGA 1800

TCTAACATTG ATCAATAACG AATTCCTAAG CATCTATATT AGTTAGCCCA GTGTTTCTCA 1860

AAGTCCACCG CATGTAAAAA TCATCTAGGG AATCTTTCTA AAATGTGGAT TCTGATTTAG 1920

TAGGTCTGGG GTGAGGTCTT CCCTTTTGCA ATTCCAGCAA GTTCCCATGG GATGCTGGTA 1980

CTGGTTAATG AAGTCACTTA GAGTAGCAAG GAGCCTGTTT GCCTAGTATT TACAATGAGC 2040

ACGTTTTGGG TATCATCAAA ACAAGAGAAT CTAAAAATGT ATGGTGTGGG TGGAAGGTTG 2100

TGTTACTTGA TATTTCAAAA AGATCATTGA AATCAGAAAA TCTCAGAGAT ATGTTGGATT 2160

TCATCACATT TATTCTATGG CTTAATGTTG TTTTATTTTG AATATATAAT AAGAGAGATA 2220

CCACAAATCT TTAGCTATTA ATATTTAGGG ATGTTAATGT CCTTAATTCA TATTGTCTCA 2280

AATGTGATTC ATTCCCTCTA TAGGTATACT AAAACAGGCA TTCATGCCTA CAAAACCATC 2340

TTCCTAACTT TCTTTCCTCT TTTTAGTCTC TTCCTGAACC AGTGACAGTG GTTCTCAAAC 2400

ATTTTGGTCT GAGGACCCCT TTATGGCCTT AAAAATGATC GAAGAGCTTT TATTTATGAA 2460

GGTAATACCT GCTAATACTT GTTGTAATCT ATTAACATTG AGAAATGTAA AAATTTTTAT 2520

TAATTCACTT AAAATATCAA TAAACCCATT ATTTGCTAAT AAAAAAAAAA AAAAAAAAAA 2580

AAAA 2584

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 42 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Phe Tyr Thr Phe Cys Glu Ser Trp Arg Ile Tyr Ile Cys Phe Thr
1 5 10 15

Met Cys Ile Ala Asn Lys Ile Ser Ile Ser Cys Ala Arg Glu Leu Asn
20 25 30

Thr Leu Ser Lys Gly His Phe Ile Thr Leu
35 40

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2233 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CTTTCCCATC TTTTGCAAAG AAACTTTTGA TCTCTCTGTG CAAAGATGTT CCCTTTCAAG 60

TTAAGTGTGT GGCCTGCCAC AAGACACTGC GTTCCCACAT GGAGCTCACT GCCCATTTCA 120

GAGTTCATTG TCGAAATGCT GGACCTGTAG CTGTAGCTGA GAAGAGCATT ACCCAGGTTG 180

CAGAGAAATT CATATTAAGA GGTTATTGTC CAGATTGCAA TCAAGTCTTT GTGGATGAAA 240

CCAGCACCCA AAATCATAAG CAGAATTCAG GACACAAAGT CCGAGTCATT AACTCAGTGG 300

AAGAATCAGT CTTACTCTAT TGCCACAGCA GCGAAGGGAA CAAGGATCCT TCTTCTGACT 360

TGCATTTATT GTTGGATCAA TCAAAATTTT CATCACTTAA AAGAACCATG TCTATTAAAG 420

AATCTAGCTC ACTGGAGTGC ATTGCCATTC CAAAAAAGAA GATGAATTTA AAAGATAAAA 480

GCCATGAAGG TGTTGCTTGT GTCCAGAAAG AAAAATCAGT AGTTAAAACC TGGTTCTGTG 540

AATGCAATCA GCGATTCCCA AGTGAAGATG CAGTAGAAAA GCATGTTTTC TCAGCAAACA 600

CAATGGGTTA TAAATGTGTG GTCTGTGGAA AGGTATGTGA TGATTCAGGG GTCATTCGTT 660

TACACATGAG CCGGATTCAC GGAGGGGCAC ATTTAAATAA CTTTCTTTTC TGGTGTCGGA 720

CATGCAAAAA GGAGTTAACA AGGAAAGATA CTATCATGGC ACATGTGACT GAATTTCATA 780

ATGGACACAG ATATTTTTAT GAGATGGATG AGGTAGAAGG TGAAACTTTG CCATCATCCT 840

CTACAACATT GGATAATTTG ACTGCTAACA AGCCTTCATC AGCTATTACT GTTATTGATC 900

ATTCCCCGGC AAATAGTTCT CCGAGGGGTA AATGGCAATG CCGGATTTGT GAAGATATGT 960

TTGATTCCCA GGAATATGTA AACAGCACTG CATGTCTTTG GCAAGCCACA AGTTTCATAG 1020

ATACAGCTGT GCTCACTGCA GAAAGCCTTT TCATAAGATA GAAACATTGT ACCGACATTG 1080

CCAAGATGAG CATGACAATG AGATAAAGAT TAAATACTTC TGTGGGCTTT GTGATCTTAT 1140

CTTTAATGTG GAAGAAGCAT TTTTGAGTCA TTATGAGGAG CACCACAGCA TAGATTATGT 1200

ATTTGTGTCA GAAAAAACTG AAACTTCAAT TAAAACCGAA GATGATTTTC CAGTAATAGA 1260

GACCAGTAAC CAGTTAACTT GTGGTTGCCG TGAGAGTTAC ATCTGTAAAG TCAACAGAAA 1320

AGAAGATTAT AGCAGATGTC TCCAAATCAT GCTGGATAAA GGAAAACTGT GGTTTCGCTG 1380

CAGTTTATGT TCGGCAACAG CACAGAATTT AACCGACATG AACACTCATA TCCATCAAGT 1440

GCACAAAGAA AAGAGTGATG AGGAGGAGCA GCAGTATGTA ATCAAGTGTG GCACCTGCAC 1500

CAAAGCATTT CATGATCCTG AGAGTGCACA GCAGCATTTC CATAGAAAAC ATTGCTTCTT 1560

ACAGAAACCC AGTGTGGCTC ATTTTGGATC TGAAAAATCA AACCTGTACA AGTTTACTGC 1620

TAGTGCCTCA CATACAGAGA GAAAACTGAA ACAGGCAATA AACTATTCAA AAAGTTTAGA 1680

CATGGAGAAA GGAGTTGAGA ATGACCTAAG CTATCAGAAT ATAGAGGAAG AAATTGTTGA 1740

GCTTCCAGAT TTGGATTACC TGCGAACCAT GACTCATATA GTCTTTGTAG ATTTTGATAA 1800

CTGGTCAAAC TTTTTTGGTC ATCTACCAGG GCATCTAAAC CAAGGAACAT TTATTTGGGG 1860

CTTTCAAGGT ACGGTTAATA AGAAAAACAA AAGAAAACTT TTTCCCACCT CTTAGAATAT 1920

AGTTCAGTTT AAAAGGCTCC TCTTAAACCT TCCTGGATAG AACATAGGAA CATAATTGGA 1980

ATATTGTTCT TTTGTATTAT AGTTACTCTG CTAGAATCGT TTTCTTTACA TGCCTCTGTG 2040

GTAAATGTTA GCTCTATCTG GTGACTCAAA GTTTATGGAT CTTTTGGCCG GGCGCGGTGG 2100

CTCACGTCTG TAATCCCAGA ACTTTGGAAG GCTGAGGCGG ACGGATCACG AGGTCAGAAG 2160

ATCGAGACCA TCCTGGCTAA CATGGTGAAA CCCCGTCTCT ACTAAAAAAA AAAAAAAAAA 2220

AAAAAAAAAA AAA 2233

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 320 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Glu Leu Thr Ala His Phe Arg Val His Cys Arg Asn Ala Gly Pro
1 5 10 15

Val Ala Val Ala Glu Lys Ser Ile Thr Gln Val Ala Glu Lys Phe Ile
20 25 30

Leu Arg Gly Tyr Cys Pro Asp Cys Asn Gln Val Phe Val Asp Glu Thr
35 40 45

Ser Thr Gln Asn His Lys Gln Asn Ser Gly His Lys Val Arg Val Ile
50 55 60

Asn Ser Val Glu Glu Ser Val Leu Leu Tyr Cys His Ser Ser Glu Gly
65 70 75 80

```
Asn Lys Asp Pro Ser Ser Asp Leu His Leu Leu Leu Asp Gln Ser Lys
                85                  90                  95

Phe Ser Ser Leu Lys Arg Thr Met Ser Ile Lys Glu Ser Ser Ser Leu
            100                 105                 110

Glu Cys Ile Ala Ile Pro Lys Lys Lys Met Asn Leu Lys Asp Lys Ser
        115                 120                 125

His Glu Gly Val Ala Cys Val Gln Lys Glu Lys Ser Val Val Lys Thr
    130                 135                 140

Trp Phe Cys Glu Cys Asn Gln Arg Phe Pro Ser Glu Asp Ala Val Glu
145                 150                 155                 160

Lys His Val Phe Ser Ala Asn Thr Met Gly Tyr Lys Cys Val Val Cys
                165                 170                 175

Gly Lys Val Cys Asp Asp Ser Gly Val Ile Arg Leu His Met Ser Arg
            180                 185                 190

Ile His Gly Gly Ala His Leu Asn Asn Phe Leu Phe Trp Cys Arg Thr
        195                 200                 205

Cys Lys Lys Glu Leu Thr Arg Lys Asp Thr Ile Met Ala His Val Thr
    210                 215                 220

Glu Phe His Asn Gly His Arg Tyr Phe Tyr Glu Met Asp Glu Val Glu
225                 230                 235                 240

Gly Glu Thr Leu Pro Ser Ser Ser Thr Thr Leu Asp Asn Leu Thr Ala
                245                 250                 255

Asn Lys Pro Ser Ser Ala Ile Thr Val Ile Asp His Ser Pro Ala Asn
            260                 265                 270

Ser Ser Pro Arg Gly Lys Trp Gln Cys Arg Ile Cys Glu Asp Met Phe
        275                 280                 285

Asp Ser Gln Glu Tyr Val Asn Ser Thr Ala Cys Leu Trp Gln Ala Thr
    290                 295                 300

Ser Phe Ile Asp Thr Ala Val Leu Thr Ala Glu Ser Leu Phe Ile Arg
305                 310                 315                 320
```

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1285 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

GGAAAGCCAT TTCTAGCACA GAAGCAGTTC TAAACAACCG ATTCATTCGA GTCTTGTGGC 60

ATAGGGAAAA TAATGAGCAA CCGACACTAC AGTCCTCAGC ACAGCTGCTC CTGCAACAAC 120

AGCAAACACT TAGTCACCTC TCACAGCAGC ACCATCACCT GCCACAGCAT CTACATCAGC 180

AGCAGGTGCT AGTGGCCCAG TCTGCTCCTT CAACAGTGCA CGGAGGTATC CAGAAGATGA 240

TGAGCAAACC ACAGACATCA GGTGCATATG TTCTTAACAA AGTTCCTGTT AAACATCGTC 300

TTGGACATGC AGGTGGTGCT GGAGAAGATT GCCAGATATT TTCAACTCCA GGCCATCCAA 360

AAATGATTTA CAGCTCCTCA AACTTAAAGA CACCTTCAAA GCTCTGTTCA GGGTCTAAAT 420

CTCATGATGT TCAAGAAGTG CTTAAAAAAA AACAGGAAGC AATGAAGTTA CAACAAGATA 480

TGAGGAAAAA AAGACAGGAA GTGTTAGAAA AGCAAATAGA ATGCCAAAAG ATGTTAATAT 540

CCAAGTTAGA AAAAAACAAA AACATGAAAC CAGAAGAAAG AGCAAATATA ATGAAGACTT 600

TGAAAGAGCT TGGAGAGAAG ATCTCACAAT TAAAAGATGA ATTAAAAACA TCTTCTGCAG 660

TCTCCACACC ATCTAAAGTG AAGACAAAAA CGGAGGCCCA GAAGGAGTTA TTAGATACTG 720

AACTGGACCT CCACAAGAGG CTGTCCTCAG GAGAAGACAC CACAGAATTA CGGAAAAAAC 780

TCAGTCAGTT ACAGGTTGAG GCTGCACGGT TAGGTATTTT ACCTGTGGGT CGAGGAAAGA 840

CCATGTCCTC TCAAGGTCGA GGAAGAGGCC GAGGGCGTGG AGGAAGAGGA AGGGGCTCAC 900

TAAATCACAT GGTGGTGGAC CATCGTCCCA AAGCACTAAC AGTTGGAGGA TTCATTGAGG 960

AAGAAAAAGA AGACTTGCTT CAGCATTTCT CAACCGCAAA CCAAGGGCCA AAATTTAAAG 1020

ACCGTCGGCT ACAGATATCA TGGCACAAGC CCAAGGTACC ATCTATATCC ACTGAGACTG 1080

AAGAAGAAGA AGTCAAGGAG GAGGAAACAG AAACCTCAGA TTTGTTTTTG CCTGATGATG 1140

ACGATGAAGA TGAAGATGAA TATGAGTCTC GCTCATGGCG AAGATGAAAT CTGATGCTAG 1200

CTGTATAATT TTTAGGAATA TTGTTTAGAA GAACAACTTT TAAAAATTAT TTAAAAGAAG 1260

TCAATGAGCC AAAAAAAAAA AAAAA 1285

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 316 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

```
Met Met Ser Lys Pro Gln Thr Ser Gly Ala Tyr Val Leu Asn Lys Val
1               5                  10                  15

Pro Val Lys His Arg Leu Gly His Ala Gly Gly Ala Gly Glu Asp Cys
            20                  25                  30

Gln Ile Phe Ser Thr Pro Gly His Pro Lys Met Ile Tyr Ser Ser Ser
        35                  40                  45

Asn Leu Lys Thr Pro Ser Lys Leu Cys Ser Gly Ser Lys Ser His Asp
    50                  55                  60

Val Gln Glu Val Leu Lys Lys Lys Gln Glu Ala Met Lys Leu Gln Gln
65                  70                  75                  80

Asp Met Arg Lys Lys Arg Gln Glu Val Leu Glu Lys Gln Ile Glu Cys
                85                  90                  95

Gln Lys Met Leu Ile Ser Lys Leu Glu Lys Asn Lys Asn Met Lys Pro
            100                 105                 110

Glu Glu Arg Ala Asn Ile Met Lys Thr Leu Lys Glu Leu Gly Glu Lys
        115                 120                 125

Ile Ser Gln Leu Lys Asp Glu Leu Lys Thr Ser Ser Ala Val Ser Thr
    130                 135                 140

Pro Ser Lys Val Lys Thr Lys Thr Glu Ala Gln Lys Glu Leu Leu Asp
145                 150                 155                 160

Thr Glu Leu Asp Leu His Lys Arg Leu Ser Ser Gly Glu Asp Thr Thr
                165                 170                 175

Glu Leu Arg Lys Lys Leu Ser Gln Leu Gln Val Glu Ala Ala Arg Leu
            180                 185                 190

Gly Ile Leu Pro Val Gly Arg Gly Lys Thr Met Ser Ser Gln Gly Arg
        195                 200                 205

Gly Arg Gly Arg Gly Arg Gly Gly Arg Gly Arg Gly Ser Leu Asn His
    210                 215                 220

Met Val Val Asp His Arg Pro Lys Ala Leu Thr Val Gly Gly Phe Ile
225                 230                 235                 240

Glu Glu Glu Lys Glu Asp Leu Leu Gln His Phe Ser Thr Ala Asn Gln
```

245 250 255

Gly Pro Lys Phe Lys Asp Arg Arg Leu Gln Ile Ser Trp His Lys Pro
260 265 270

Lys Val Pro Ser Ile Ser Thr Glu Thr Glu Glu Glu Glu Val Lys Glu
275 280 285

Glu Glu Thr Glu Thr Ser Asp Leu Phe Leu Pro Asp Asp Asp Asp Glu
290 295 300

Asp Glu Asp Glu Tyr Glu Ser Arg Ser Trp Arg Arg
305 310 315

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2346 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CACGCGAGGC GCTGTCCTTT CAGCACCACA AGCTCGGGCT GAGGAGGGAG GACTCCTGGC 60

CGTCCTCCTC CTCTTCAAAT TGGCTTGAAT CTGCTCTGAC CCCCCACGAG TGCAGCACAG 120

TCTGGGAAGA AAGGCGTAAG GATGGTGAAG CTGAACAGTA ACCCCAGCGA GAAGGGAACC 180

AAGCCGCCTT CAGTTGAGGA TGGCTTCCAG ACCGTCCCTC TCATCACTCC CTTGGAGGTT 240

AATCACTTAC AGCTGCCTGC TCCAGAAAAG GTGATTGTGA AGACAAGAAC GGAATATCAG 300

CCGGAACAGA AGAACAAAGG GAAGTTCCGG GTGCCGAAAA TCGCTGAATT TACGGTCACC 360

ATCCTTGTCA GCCTGGCCCT AGCTTTCCTT GCGTGCATCG TGTTCCTGGT GGTTTACAAA 420

GCCTTCACCT ATGATCACAG CTGCCCAGAG GGATTCGTCT ATAAGCACAA ACGCTGTATC 480

CCAGCCTCCC TGGATGCTTA CTACTCCTCC CAGGACCCCA ATTCCAGAAG CCGCTTCTAC 540

ACAGTCATCA GCCACTACAG CGTGGCCAAG CAGAGCACTG CCCGGGCCAT CGGGCCGTGG 600

CTGTCAGCAG CCGCTGTCAT CCATGAGCCC AAGCCGCCCA AGAACCCAGG GCCACTAAAG 660

GCCTGCCCCA GCCAAAATGG GGGGCGGGGT GGAAAGGAGG ACCCCCATTG GCTAACCCAA 720

GCTCCAGTTA CAAAACAACA CTGTACTCCT GGGATATGGG GGCGGGGGCG GGGCAGGGCA 780

GGGTGGGGGG AAAAACGCAC CAAAAACGTG GTGTGTGCTG GAGTTGTCTG AACCGATATT 840

TCTTTTTGTT CCTTGGTATT GTTGATTCGT CGCCGAGTCA GGCTCATGTA CAAAGGCATG 900

TTTCGTGTTG ATTGTTCCCA TGTAAGATAT TTTTAAAGCC ACTGCTTATT CTTTGTTAGG 960

AAAATGTAAC AGCAGAAAAG GAAAGAAACA AAGAACATGA ACAAAAAGCA TTAAACTGGC 1020

TCCATCAGAA GACGTTGAAG GGCAGTGAAG AGCACAGACT CTGTGGGCTT CTTAGATAAG 1080

AAAACGTAGC TTCAGTGGGG GCTCCAGGGT TGCAGAGTAT GAGTGACACA GACCGGGACT 1140

ATTCCATTAG CCTGTGGTCT GCAGGGTAGG CCCGCAGGAA ATGAGGAATG GCCGAGCTGG 1200

AGAGAAGAGC TGATTTTGGC ATTACTAAGC CCAGAACGCA CATAACCCAT AGTGAAATGT 1260

GCTGGCCTCT GGTGCATTTT GCAAGATGAG CACAAACTTT CTGGGCCTCC ATCCTAGGAC 1320

CTGGGCAGAC CCACATGGCC TGGGCTTTGA ATGCCCACCC TGCGACGGTG GGTTTTGCAT 1380

CAGCAAACGC TGAGGAGTGG GCAGATTTTT TTTGTTTTTT GCTTGCATTT TTTAGATCCA 1440

CACCTGGATA CTGCCCATGT TGACGAGACA GCAGCAGGGG GAGAGGGAGG GAAGGAAGGT 1500

GCGGCTGCAA GAAGGAAGGC ACGGGACAGG CATGTGACAC TAGGCCACAA GCGATAAGCA 1560

CAGGCACCTG ACTTTTAAGT TTTTGTTTGT TTGTTGTTTC CCAAAGTGCT GATAACAATA 1620

ACAACAACAA TAGGATTCCA ACCAGGAGCC TCAAGTGACA GCCAGGAAGA GACCTGAAGG 1680

TTGGGGCCAC CACAATGCCA AATCGTTTCT AAAGGAAGCT GAAAAATGGG ACTGTCTTTT 1740

GCCCACTTCG TTGTGTTAAA AGGGGACATT TGTCCAAACT CCCCAACCGA GTTTTAGAAG 1800

CTCCTGACAA GGAGGCAGCA TCCAGCCTTG ACCAGGCCTC CCAGTTCCCT GGAACCGTAT 1860

CAGGCATTCG CCTGCCTCTC ACAAATGTTT CAGGGAGGCC AGTTCTGCAG GGTGTCAGCT 1920

CCAGGACCCA CAGGGCCAGA ACCAGCTGGG AGAATTGGTT ATTTGAGATG TGGTACTGCT 1980

TCCTCACAAG TCTCCCACAG GCCATGTAAA GGGTATTTTT TTGTGGCTTG CTGTGTTGCT 2040

GAGATCATCG TATGCAACAG CTGGGTAATA AGACTAGCAT AGCTCAAACT ATCCTGCCAA 2100

ACGCTCTCAT ATGATTTTTC CTCCCTTCTC CCCCAACCTC CAATCACCCT GAGTCACCTG 2160

TAAATTCATT TGTCATTCAA AGCGGAATAA CAAGTTGTCC CTAGCAAAAC CGCTGAGCGC 2220

TTTATAATTT TGTGGTGTAT TTTTGTCAGT AGGTAGCAGA GGCGGAAGTA TTTTTTGGTG 2280

TAATTCTTGA AATTTTCTGA CAGGAAACAA ATAAAGATAG ATGTGTCTGA GAAAAAAAAA 2340

AAAAAA 2346

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 229 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```
Met Val Lys Leu Asn Ser Asn Pro Ser Glu Lys Gly Thr Lys Pro Pro
1               5                  10                  15

Ser Val Glu Asp Gly Phe Gln Thr Val Pro Leu Ile Thr Pro Leu Glu
            20                  25                  30

Val Asn His Leu Gln Leu Pro Ala Pro Glu Lys Val Ile Val Lys Thr
        35                  40                  45

Arg Thr Glu Tyr Gln Pro Glu Gln Lys Asn Lys Gly Lys Phe Arg Val
    50                  55                  60

Pro Lys Ile Ala Glu Phe Thr Val Thr Ile Leu Val Ser Leu Ala Leu
65                  70                  75                  80

Ala Phe Leu Ala Cys Ile Val Phe Leu Val Val Tyr Lys Ala Phe Thr
                85                  90                  95

Tyr Asp His Ser Cys Pro Glu Gly Phe Val Tyr Lys His Lys Arg Cys
            100                 105                 110

Ile Pro Ala Ser Leu Asp Ala Tyr Tyr Ser Ser Gln Asp Pro Asn Ser
        115                 120                 125

Arg Ser Arg Phe Tyr Thr Val Ile Ser His Tyr Ser Val Ala Lys Gln
    130                 135                 140

Ser Thr Ala Arg Ala Ile Gly Pro Trp Leu Ser Ala Ala Ala Val Ile
145                 150                 155                 160

His Glu Pro Lys Pro Pro Lys Asn Pro Gly Pro Leu Lys Ala Cys Pro
                165                 170                 175

Ser Gln Asn Gly Gly Arg Gly Gly Lys Glu Asp Pro His Trp Leu Thr
            180                 185                 190

Gln Ala Pro Val Thr Lys Gln His Cys Thr Pro Gly Ile Trp Gly Arg
        195                 200                 205

Gly Arg Gly Arg Ala Gly Trp Gly Glu Lys Arg Thr Lys Asn Val Val
    210                 215                 220
```

Cys Ala Gly Val Val
225

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2104 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

GGATGAGTCT CAAGATGGAC AACCGGGATG TTGCAGGAAA GGCTAACCGG TGGTTTGGGG 60

TTGCTCCCCC TAAATCTGGA AAAATGAACA TGAACATCCT TCACCAGGAA GAGCTCATCG 120

CTCAGAAGAA ACGGGAAATT GAAGCCAAAA TGGAACAGAA AGCCAAGCAG AATCAGGTGG 180

CCAGCCCTCA GCCCCCACAT CCTGGCGAAA TCACAAATGC ACACAACTCT TCCTGCATTT 240

CCAACAAGTT TGCCAACGAT GGTAGCTTCT TGCAGCAGTT TCTGAAGTTG CAGAAGGCAC 300

AGACCAGCAC AGACGCCCCG ACCAGTGCGC CCAGCGCCCC TCCCAGCACA CCCACCCCCA 360

GCGCTGGGAA GAGGTCCCTG CTCATCAGCA GGCGGACAGG CCTGGGGCTG GCCAGCCTGC 420

CGGGCCCTGT GAAGAGCTAC TCCCACGCCA AGCAGCTGCC CGTGGCGCAC CGCCCGAGTG 480

TCTTCCAGTC CCCTGACGAG GACGAGGAGG AGGACTATGA GCAGTGGCTG GAGATCAAAG 540

TTTCACCCCC AGAGGGAGCC GAGACTCGGA AAGTGATAGA GAAATTGGCC CGCTTTGTGG 600

CAGAAGGAGG CCCCGAGTTA GAAAAAGTAG CTATGGAGGA CTACAAGGAT AACCCAGCAT 660

TTGCATTTTT GCACGATAAG AATAGCAGGG GATTCCTCTA CTACAGGAAG AAGGTGGCTG 720

AGATAAGAAA GGAAGCACAG AAGTCGCAGG CAGCCTCTCA GAAAGTTTCA CCCCCAGAGG 780

ACGAAGAGGT CAAGAACCTT GCAGAAAAGT TGGCCAGGTT CATAGCGGAC GGGGGTCCCG 840

AGGTGGAAAC CATTGCCCTC CAGAACAACC GTGAGAACCA GGCATTCAGC TTTCTGTATG 900

AGCCCAATAG CCAAGGGTAC AAGTACTACC GACAGAAGCT GGAGGAGTTC CGGAAAGCCA 960

AGGCCAGCTC CACAGGCAGC TTCACAGCAC CTGATCCCGG CCTGAAGCGC AAGTCCCCTC 1020

CTGAGGCCCT GTCAGGGTCC TTACCCCCAG CCACCACCTG CCCCGCCTCG TCCACGCCTG 1080

CGCCCACTAT CATCCCTGCT CCAGCTGCCC CCGGGAAGCC AGCCTCCGCA GCCACCGTGA 1140

AGAGGAAGCG GAAGAGCCGG TGGGGGCCTG AAGAGGATAA GGTAGAGCTC CCACCTGCTG 1200

AACTGGTGCA GAGGGACGTG GATGCCTCTC CCTCGCCTCT GTCAGTTCAG GACCTCAAGG 1260

GGCTCGGCTA TGAGAAGGGG AAGCCTGTGG GTCTAGTGGG CGTCACAGAG CTTTCAGACG 1320

CCCAGAAGAA GCAGCTGAAG GAGCAGCAGG AGATGCAGCA GATGTACGAC ATGATCATGC 1380

AGCACAAGCG GGCCATGCAG GACATGCAGC TGCTGTGGGA GAAGGCAGTC CAACAGCACC 1440

AGCACGGCTA TGACAGTGAT GAGGAGGTGG ACAGCGAGCT GGGCACCTGG GAGCACCAGC 1500

TGCGGCGCAT GGAGATGGAT AAGACCAGGG AATGGGCCGA GCAGCTGACA AAGATGGGCC 1560

GGGGCAAGCA CTTCATCGGA GACTTCCTGC CTCCAGACGA GCTGGAAAAG TTTATGGAGA 1620

CCTTCAAGGC CCTGAAGGAG GGCCGTGAGC CTGACTACTC AGAGTACAAG GAGTTCAAGC 1680

TGACTGTGGA GAACATCGGC TACCAGATGT TGATGAAGAT GGGCTGGAAG GAGGGCGAGG 1740

GGCTGGGCTC AGAGGGCCAG GGCATCAAGA ACCCAGTGAA CAAGGGCACC ACCACAGTGG 1800

ACGGCGCTGG CTTCGGCATT GACCGGCCGG CGGAGCTCTC CAAGGAGGAC GACGAGTATG 1860

AGGCGTTCCG CAAGAGGATG ATGCTGGCCT ACCGCTTCCG GCCCAACCCC CTGAACAATC 1920

CCAGACGGCC TTACTACTGA GTGTTCTGGA AATACATACT TTCTGAATGA CCAACCGTCC 1980

CTGGACTGTG GAATGTTCCG GCCTGCATTT CTGCCCACCC CTTCCGTTGT CACGAGTGCC 2040

GTGCCGTGTA ATAAAGTCCC AGTGCTCATC CAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 2100

AAAA 2104

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 645 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Met Ser Leu Lys Met Asp Asn Arg Asp Val Ala Gly Lys Ala Asn Arg
1 5 10 15

Trp Phe Gly Val Ala Pro Pro Lys Ser Gly Lys Met Asn Met Asn Ile
20 25 30

```
Leu His Gln Glu Glu Leu Ile Ala Gln Lys Lys Arg Glu Ile Glu Ala
        35                  40                  45

Lys Met Glu Gln Lys Ala Lys Gln Asn Gln Val Ala Ser Pro Gln Pro
    50                  55                  60

Pro His Pro Gly Glu Ile Thr Asn Ala His Asn Ser Ser Cys Ile Ser
65                  70                  75                  80

Asn Lys Phe Ala Asn Asp Gly Ser Phe Leu Gln Gln Phe Leu Lys Leu
                85                  90                  95

Gln Lys Ala Gln Thr Ser Thr Asp Ala Pro Thr Ser Ala Pro Ser Ala
            100                 105                 110

Pro Pro Ser Thr Pro Thr Pro Ser Ala Gly Lys Arg Ser Leu Leu Ile
        115                 120                 125

Ser Arg Arg Thr Gly Leu Gly Leu Ala Ser Leu Pro Gly Pro Val Lys
    130                 135                 140

Ser Tyr Ser His Ala Lys Gln Leu Pro Val Ala His Arg Pro Ser Val
145                 150                 155                 160

Phe Gln Ser Pro Asp Glu Asp Glu Glu Glu Asp Tyr Glu Gln Trp Leu
                165                 170                 175

Glu Ile Lys Val Ser Pro Pro Glu Gly Ala Glu Thr Arg Lys Val Ile
            180                 185                 190

Glu Lys Leu Ala Arg Phe Val Ala Glu Gly Gly Pro Glu Leu Glu Lys
        195                 200                 205

Val Ala Met Glu Asp Tyr Lys Asp Asn Pro Ala Phe Ala Phe Leu His
    210                 215                 220

Asp Lys Asn Ser Arg Gly Phe Leu Tyr Tyr Arg Lys Lys Val Ala Glu
225                 230                 235                 240

Ile Arg Lys Glu Ala Gln Lys Ser Gln Ala Ala Ser Gln Lys Val Ser
                245                 250                 255

Pro Pro Glu Asp Glu Glu Val Lys Asn Leu Ala Glu Lys Leu Ala Arg
            260                 265                 270

Phe Ile Ala Asp Gly Gly Pro Glu Val Glu Thr Ile Ala Leu Gln Asn
        275                 280                 285

Asn Arg Glu Asn Gln Ala Phe Ser Phe Leu Tyr Glu Pro Asn Ser Gln
    290                 295                 300

Gly Tyr Lys Tyr Tyr Arg Gln Lys Leu Glu Glu Phe Arg Lys Ala Lys
305                 310                 315                 320

Ala Ser Ser Thr Gly Ser Phe Thr Ala Pro Asp Pro Gly Leu Lys Arg
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325 330 335

Lys Ser Pro Pro Glu Ala Leu Ser Gly Ser Leu Pro Pro Ala Thr Thr
340 345 350

Cys Pro Ala Ser Ser Thr Pro Ala Pro Thr Ile Ile Pro Ala Pro Ala
355 360 365

Ala Pro Gly Lys Pro Ala Ser Ala Ala Thr Val Lys Arg Lys Arg Lys
370 375 380

Ser Arg Trp Gly Pro Glu Glu Asp Lys Val Glu Leu Pro Pro Ala Glu
385 390 395 400

Leu Val Gln Arg Asp Val Asp Ala Ser Pro Ser Pro Leu Ser Val Gln
405 410 415

Asp Leu Lys Gly Leu Gly Tyr Glu Lys Gly Lys Pro Val Gly Leu Val
420 425 430

Gly Val Thr Glu Leu Ser Asp Ala Gln Lys Lys Gln Leu Lys Glu Gln
435 440 445

Gln Glu Met Gln Gln Met Tyr Asp Met Ile Met Gln His Lys Arg Ala
450 455 460

Met Gln Asp Met Gln Leu Leu Trp Glu Lys Ala Val Gln Gln His Gln
465 470 475 480

His Gly Tyr Asp Ser Asp Glu Glu Val Asp Ser Glu Leu Gly Thr Trp
485 490 495

Glu His Gln Leu Arg Arg Met Glu Met Asp Lys Thr Arg Glu Trp Ala
500 505 510

Glu Gln Leu Thr Lys Met Gly Arg Gly Lys His Phe Ile Gly Asp Phe
515 520 525

Leu Pro Pro Asp Glu Leu Glu Lys Phe Met Glu Thr Phe Lys Ala Leu
530 535 540

Lys Glu Gly Arg Glu Pro Asp Tyr Ser Glu Tyr Lys Glu Phe Lys Leu
545 550 555 560

Thr Val Glu Asn Ile Gly Tyr Gln Met Leu Met Lys Met Gly Trp Lys
565 570 575

Glu Gly Glu Gly Leu Gly Ser Glu Gly Gln Gly Ile Lys Asn Pro Val
580 585 590

Asn Lys Gly Thr Thr Thr Val Asp Gly Ala Gly Phe Gly Ile Asp Arg
595 600 605

Pro Ala Glu Leu Ser Lys Glu Asp Asp Glu Tyr Glu Ala Phe Arg Lys
610 615 620

Arg Met Met Leu Ala Tyr Arg Phe Arg Pro Asn Pro Leu Asn Asn Pro
625 630 635 640

Arg Arg Pro Tyr Tyr
645

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1642 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CAAGTTTTGT TGTGCTGATT TAACAGCCTG TGAATTCTGC AAACACGATC GTGAAAAAAT 60

GCCAATCTGT CCTGTGTAAG VCCTGTGTGA AGTTTTGACT TTAATCTACC AGATCACTCC 120

TTCACCCTCC ATAAAGATGT CTGAACCTGA CACTTCCTCA GGATTTTCGG GAAGTGTGGA 180

GAATGGAACT TTTCTTGAGC TGTTTCCCAC ATCCCTGTCC ACGTCAGTGG ACCCATCCTC 240

AGGCCACCTG TCAAACGTCT ACATCTATGT GTCCATATTC CTCAGCCTTT TAGCGTTTCT 300

GCTTCTGCTT TTAATCATTG CCCTCCAGAG GCTCAAAAAT ATCATCTCCT CCAGTTCCTC 360

CTACCCAGAG TATCCAAGCG ACGCTGGAAG TTCTTTCACC AATTTGGAAG TCTGCAGCAT 420

TTCCTCTCAG AGGTCCACTT TTTCAAACCT TTCATCCTGA GGAAAATGGA AGAGTCCTTG 480

AGTGTGGCAG CAGTTTTGAC ATCCCCTTAC GGAAGTGTCC CGTGAGGCAT TGCCTCATGA 540

AAGAAATGAT CCTTTTGGTG TAGACCTGCT TCTCCTTCTC CTTTTTCTCT GATTTCTTTT 600

CTGTTCATGA TGCTTTTCAT TTGGGGATGG AGACACCGAT GTTGGTGGAA ATGTGTGCAA 660

ACCCCAAGGT GCAGAATTTC ACACAAATGG CTTGATGAAT CTAGACTGGG CTTCTTCAGG 720

TAAGTCAGTT CATTCTACTT TGTTGGACGC CGTAGACTCA TCTGAGGTGG CCTCTCCGTG 780

GATGCTGGAC ATGGACTCGC ACTTCATTTC TTTTACAAAG CCGTGAAATC AACTGAGCCT 840

GCAGAAACTG GCAAAATCAA GTCTGACCTA TGTAGAAGTT ATTTTCCATA TTTAAAAGAT 900

AAAGTGGAGA CACCAAACTT AAAAAGGAAG AGAGTCAATT TAGATTTAAT GTATGACATT 960

TCTAAAACTG AGGGTAAATA TATGCTAAAT ATTTTCTTTA ACTTCACTTT AACAAGTAAA 1020

AATCACACTT ATTGATGAAT GTAAGTCATT TGGGAAAGTT TTGGAAGAGT TTACATTTTA 1080

ATAGCAAGAC AAACATGTAT TATGATGGAG CTTGTGATGT ATTTCTGCCT CCTGGAGTTT 1140

TATTTTGTTT TTCTGCTTAT GTTTTAGTCA TAATGCCACA AAGTTGTGGA ATTTTTGTGA 1200

TTAATTGCTG TTACTAGTAC TAAGAGAAGC ACCAGAAGAG ATGCCAAGAA GTTTTTATAT 1260

GAATAATTTC TATCAGTGAG AATTAAGCAT ATGGAAAATA TTCATTTAGT TGTATTTTAT 1320

ACAGTAATAA CTCTTAGCTG TCGTGTAAGT TCCTTTATTC GGTTTCATAG TCTTTATAAT 1380

TTTAGTGCAG AATTATATTA AGCCTCCAAG ATGTCTGATA TTTGTTCACT CACATTAGGT 1440

TGTAAAACTT AGAAACTAAA TTGCAAATAT ATGTGTTATT ATATACTCCA CGAATGTTGC 1500

GTCTCTGATA ATTAGTTGTT GTATGTTAAC ATAATACTCT ACATTAGGAT TTCAGGATGT 1560

GAGTTTGTAT TAAAAATTGT AGGCACTCCA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1620

AAAAAAAAAA AAAAAAAAAA AA 1642

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Ser Glu Pro Asp Thr Ser Ser Gly Phe Ser Gly Ser Val Glu Asn
1 5 10 15

Gly Thr Phe Leu Glu Leu Phe Pro Thr Ser Leu Ser Thr Ser Val Asp
20 25 30

Pro Ser Ser Gly His Leu Ser Asn Val Tyr Ile Tyr Val Ser Ile Phe
35 40 45

Leu Ser Leu Leu Ala Phe Leu Leu Leu Leu Leu Ile Ile Ala Leu Gln
50 55 60

Arg Leu Lys Asn Ile Ile Ser Ser Ser Ser Ser Tyr Pro Glu Tyr Pro
65 70 75 80

Ser Asp Ala Gly Ser Ser Phe Thr Asn Leu Glu Val Cys Ser Ile Ser
85 90 95

Ser Gln Arg Ser Thr Phe Ser Asn Leu Ser Ser
100 105

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1365 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

CGCAGGAAGC AGAAGAGCAG AGCGAGGACG ACGACGAGGA TACAGAAGAG GAACAGGGGG 60

AAGAAAAGGA AAAGGGAGCG CAGGAGAAAA GGAGGGGGAA GAGAGTCCGT TTTGCAGAAG 120

ATGAAGAAAA GAGTGAAAAT TCCTCGGAGG ACGGTGACAT AACGGATAAG AGTCTTTGTG 180

GAAGTGGTGA AAAGTACATC CCACCTCATG TGAGGCAAGC TGAGGAGACA GTGGACTTCA 240

AGAAAAAGGA AGAACTAGAA AGGCTGAAGA AACATGTAAA AGGTCTACTT AACAGGTTGA 300

GTGAACCCAA CATGGCTTCC ATCAGTGGGC AGCTGGAGGA ACTGTACATG GCCCACAGCA 360

GAAAGGACAT GAATGACACC CTGACCTCCG CTCTCATGGG TGCCTGCGTC ACTGCCTCGG 420

CCATGCCCAG CAGACTGATG ATGGAGCATG TTCTCTTAGT CAGCATCCTT CACCACACAG 480

TTGGAATCGA GGTCGGTGCC CACTTTCTGG AGGCAGTGGT GAGGAAGTTC GATGCCATCT 540

ATAAATACGG AAGCGAAGGG AAAGAGTGTG ACAACCTGTT CACCGTCATT GCCCATTTAT 600

ACAACTTCCA CGTGGTACAG TCTCTCCTCA TCTTCGACAT TTTGAAAAAA CTGATTGGAA 660

CTTTCACCGA AAAAGATATT GAACTGATCT TGTTAATGCT GAAAAACGTG GGTTTTTCAT 720

TGAGGAAAGA TGATGCTTTA TCACTTAAGG AATTGATCAC TGAAGCCCAG ACCAAAGCCA 780

GCGGGGCAGG CAGCGAGTTT CAGGACCAGA CCAGGGTACG CGTGCGACGC TTGATCTGCT 840

TCCTAAGTCC CTAAAGCTCA CAAACTGGCC AGAACCTAAA AATCAGTATC TGGGATTCGG 900

TTTATGCTAG AGACGATGTT GGCCCTGAAG AACAATGACA TGCGCAAAAT TCCAGGCTAT 960

GACCCCGAGC CCGTGGAGAA GCTGAGGAAA CTGCAGAGAG CTTTGGTCCG CAACGCCGGC 1020

TCAGGTTCTG AGACGCAGCT TCGCGTCTCC TGGGACAGTG TCTTGAGTGC GGAGCAGACG 1080

GGTCGCTGGT GGATTGTGGG GTCCGCCTGG AGTGGGGCCC CGATGATCGA CAACAGTCAC 1140

CATACGCACC TGCAGAAGCA GYTTGTGGGG ACGGTAGGGA CACCCATGYT CAAGGYTGCC 1200

AGGCAGAGGC ACCCCCCTGT GTGGTGTGTG GTCCTGGCTT TACCTGGAGC AGCTCTCTTA 1260

CTGTTCTTGA ATGGTCACTG AAATGTACAA GGTTTATCTG GAGGCCTTAC AGAAATTGCT 1320

ATTAATATTA CATTGTGATA TAATTATTCC AAAAAAAAAA AAAAA 1365

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 180 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

Met Ala Ser Ile Ser Gly Gln Leu Glu Glu Leu Tyr Met Ala His Ser
1 5 10 15

Arg Lys Asp Met Asn Asp Thr Leu Thr Ser Ala Leu Met Gly Ala Cys
20 25 30

Val Thr Ala Ser Ala Met Pro Ser Arg Leu Met Met Glu His Val Leu
35 40 45

Leu Val Ser Ile Leu His His Thr Val Gly Ile Glu Val Gly Ala His
50 55 60

Phe Leu Glu Ala Val Val Arg Lys Phe Asp Ala Ile Tyr Lys Tyr Gly
65 70 75 80

Ser Glu Gly Lys Glu Cys Asp Asn Leu Phe Thr Val Ile Ala His Leu
85 90 95

Tyr Asn Phe His Val Val Gln Ser Leu Leu Ile Phe Asp Ile Leu Lys
100 105 110

Lys Leu Ile Gly Thr Phe Thr Glu Lys Asp Ile Glu Leu Ile Leu Leu
115 120 125

Met Leu Lys Asn Val Gly Phe Ser Leu Arg Lys Asp Asp Ala Leu Ser
130 135 140

Leu Lys Glu Leu Ile Thr Glu Ala Gln Thr Lys Ala Ser Gly Ala Gly
145 150 155 160

Ser Glu Phe Gln Asp Gln Thr Arg Val Arg Val Arg Arg Leu Ile Cys
165 170 175

Phe Leu Ser Pro
180

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1310 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

CAAGCACCAG GAAGTCAAGA TGCAAGCACC AGCCTTCAGG GACAAGAAAC AGGGGGTCTC 60

AGCCAAGAAT CAAGGTGCCC ATGACCCAGA CTATGAGAAT ATCACCTTGG CCTTCAAAAA 120

TCAGGACCAT GCAAAGGGTG GTCATTCACG ACCCACGAGC CAAGTCCCAG CCCAGTGCAG 180

GCCGCCCTCA GACTCCACCC AGGTCCCCTG CTGGTTGTAC AGAGCCATCC TGAGCCTGTA 240

CATCCTCCTG GCCCTGGCCT TTGTCCTCTG CATCATCCTG TCAGCCTTCA TCATGGTGAA 300

GAATGCTGAG ATGTCCAAGG AGCTGCTGGG CTTTAAAAGG GAGCTTTGGA ATGTCTCAAA 360

CTCCGTACAA GCATGCGAAG AGAGACAGAA GAGAGGCTGG GATTCCGTTC AGCAGAGCAT 420

CACCATGGTC AGGAGCAAGA TTGATAGATT AGAGACGACA TTAGCAGGCA TAAAAAACAT 480

TGACACAAAG GTACAGAAAA TCTTGGAGGT GCTGCAGAAA ATGCCACAGT CCTCACCTCA 540

ATAAATGAGA GGACATTGTG GCAGCCAAAG CCACAACTTG GAAGATGGGG CTGCACCTGC 600

CAACGAAGAC GGGAAATGAC CCCCCCCCCC AGCCTAGTGT GAACCTGCCC CTCGTCCCAC 660

GTATAGAAAA ACCTCGAGTC ATGGTGAATG AGTGTCTCGG AGTTGCTCGT GTGTGTGTAC 720

ACCTGCGTGC GTGTGTGTGC GTGTGTGCGC GTGTGTTCGT GTATGTGCGT GTGTGCGTGC 780

GCGTGTGTGT GCATTTTGCA AAGGGTGGAC ATTTCAGTGT ATCTCCCAGA AAGGTGAKGA 840

ATGAATAGGA CTGAGAGTCA CAGTGAATGT GGCATGCATG CCTGTGTCAT GWGACATATG 900

TGAGTCTCGG CATGTCACGG TGGGTGGCTG TGTYTGAGCA CCTCCAGCAG ATGTCACTCT 960

GAGTGTGGGT GTTGGTGACA TGCATTGCAC GGGCCTGTCT CCCTGTTTGT GTAAACATAC 1020

TAGAGTATAC TGCGGCGTGT TTTCTGTCTA CCCATGTCAT GGTGGGGGAG ATTTATCTCC 1080

GWACATGTGG GTGTCGCCAT GTGTGCCCTG TCACTATCTG TGGCTGGGTG AACGGCTGTG 1140

TCATTATGAG TGTGCCGAGT TATGCCACCC TGTGTGCTCA GGGCACATGC ACACAGACAT 1200

TTATYTYTGC ACTCACATTT TGTGACTTAT GAAGATAAAT AAAGTCAAGG GAAAACAGCG 1260

TCMAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA 1310

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 174 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Gln Ala Pro Ala Phe Arg Asp Lys Lys Gln Gly Val Ser Ala Lys
1 5 10 15

Asn Gln Gly Ala His Asp Pro Asp Tyr Glu Asn Ile Thr Leu Ala Phe
20 25 30

Lys Asn Gln Asp His Ala Lys Gly Gly His Ser Arg Pro Thr Ser Gln
35 40 45

Val Pro Ala Gln Cys Arg Pro Pro Ser Asp Ser Thr Gln Val Pro Cys
50 55 60

Trp Leu Tyr Arg Ala Ile Leu Ser Leu Tyr Ile Leu Leu Ala Leu Ala
65 70 75 80

Phe Val Leu Cys Ile Ile Leu Ser Ala Phe Ile Met Val Lys Asn Ala
85 90 95

Glu Met Ser Lys Glu Leu Leu Gly Phe Lys Arg Glu Leu Trp Asn Val
100 105 110

Ser Asn Ser Val Gln Ala Cys Glu Glu Arg Gln Lys Arg Gly Trp Asp
115 120 125

Ser Val Gln Gln Ser Ile Thr Met Val Arg Ser Lys Ile Asp Arg Leu
130 135 140

Glu Thr Thr Leu Ala Gly Ile Lys Asn Ile Asp Thr Lys Val Gln Lys
145 150 155 160

Ile Leu Glu Val Leu Gln Lys Met Pro Gln Ser Ser Pro Gln
165 170

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

GNGGCATCAGA CATTGGGGAG TGATTCAA 29

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

CNTGAGAGAAC CTTTGCTTCC TGCTATAT 29

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

CNATGCACTCC AGTGAGCTAG ATTCTTTA 29

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

TNAATTGTGAG ATCTTCTCTC CAAGCTCT 29

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

GNCGGTCTGGA AGCCATCCTC AACTGAAG 29

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

ANCTCTTCCTG GTGAAGGATG TTCATGTT 29

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

CNTTATGGAGG GTGAAGGAGT GATCTGGT 29

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

ANGTCCACTGT CTCCTCAGCT TGCCTCAC 29

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

GNTTGCATCTT GACTTCCTGG TGCTTGTA 29

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 307 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

```
Met Ser Leu Ala Ser His Lys Phe His Arg Tyr Ser Cys Ala His Cys
1               5                  10                  15

Arg Lys Pro Phe His Lys Ile Glu Thr Leu Tyr Arg His Cys Gln Asp
            20                  25                  30

Glu His Asp Asn Glu Ile Lys Ile Lys Tyr Phe Cys Gly Leu Cys Asp
        35                  40                  45

Leu Ile Phe Asn Val Glu Glu Ala Phe Leu Ser His Tyr Glu Glu His
    50                  55                  60

His Ser Ile Asp Tyr Val Phe Val Ser Glu Lys Thr Glu Thr Ser Ile
65                  70                  75                  80

Lys Thr Glu Asp Asp Phe Pro Val Ile Glu Thr Ser Asn Gln Leu Thr
                85                  90                  95

Cys Gly Cys Arg Glu Ser Tyr Ile Cys Lys Val Asn Arg Lys Glu Asp
            100                 105                 110

Tyr Ser Arg Cys Leu Gln Ile Met Leu Asp Lys Gly Lys Leu Trp Phe
        115                 120                 125

Arg Cys Ser Leu Cys Ser Ala Thr Ala Gln Asn Leu Thr Asp Met Asn
    130                 135                 140

Thr His Ile His Gln Val His Lys Glu Lys Ser Asp Glu Glu Glu Gln
145                 150                 155                 160

Gln Tyr Val Ile Lys Cys Gly Thr Cys Thr Lys Ala Phe His Asp Pro
                165                 170                 175

Glu Ser Ala Gln Gln His Phe His Arg Lys His Cys Phe Leu Gln Lys
            180                 185                 190

Pro Ser Val Ala His Phe Gly Ser Glu Lys Ser Asn Leu Tyr Lys Phe
        195                 200                 205

Thr Ala Ser Ala Ser His Thr Glu Arg Lys Leu Lys Gln Ala Ile Asn
    210                 215                 220

Tyr Ser Lys Ser Leu Asp Met Glu Lys Gly Val Glu Asn Asp Leu Ser
225                 230                 235                 240
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```
Tyr Gln Asn Ile Glu Glu Glu Ile Val Glu Leu Pro Asp Leu Asp Tyr
                245                 250                 255

Leu Arg Thr Met Thr His Ile Val Phe Val Asp Phe Asp Asn Trp Ser
            260                 265                 270

Asn Phe Phe Gly His Leu Pro Gly His Leu Asn Gln Gly Thr Phe Ile
        275                 280                 285

Trp Gly Phe Gln Gly Thr Val Asn Lys Lys Asn Lys Arg Lys Leu Phe
    290                 295                 300

Pro Thr Ser
305
```

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 61 to nucleotide 642;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 89 to nucleotide 440;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BI164_1 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

2. A composition of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.

3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein encoded by a composition of claim 2, which process comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying said protein from the culture.

6. A protein produced according to the process of claim 5.

7. The protein of claim 6 comprising a mature protein.

8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 23 to amino acid 127;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone BI164_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.

10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 23 to amino acid 127.

11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.

14. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1625 to nucleotide 1750;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1484 to nucleotide 1729;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BK445_1 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 35;

(c) fragments of the amino acid sequence of SEQ ID NO:4; and

(d) the amino acid sequence encoded by the cDNA insert of clone BK445_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 99 to nucleotide 1058;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 1 to nucleotide 644;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BP101_2 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 1 to amino acid 182;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone BP101_2 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 237 to nucleotide 1184;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 207 to nucleotide 935;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CD124_3 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 1 to amino acid 233;

(c) fragments of the amino acid sequence of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone CD124_3 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 142 to nucleotide 828;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:9 from nucleotide 1 to nucleotide 522;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CW924_1 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:10;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:10 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:10;

(b) the amino acid sequence of SEQ ID NO:10 from amino acid 1 to amino acid 127;

(c) fragments of the amino acid sequence of SEQ ID NO:10; and

(d) the amino acid sequence encoded by the cDNA insert of clone CW924_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:9.

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 3 to nucleotide 1937;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:11 from nucleotide 204 to nucleotide 414;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DF518_3 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:12;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:12 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:12;

(b) the amino acid sequence of SEQ ID NO:12 from amino acid 67 to amino acid 137;

(c) fragments of the amino acid sequence of SEQ ID NO:12; and

(d) the amino acid sequence encoded by the cDNA insert of clone DF518_3 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:11.

29. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 137 to nucleotide 457;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 323 to nucleotide 457;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 82 to nucleotide 322;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DM406_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

30. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 62;

(c) fragments of the amino acid sequence of SEQ ID NO:14; and

(d) the amino acid sequence encoded by the cDNA insert of clone DM406_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.

32. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 312 to nucleotide 851;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 56 to nucleotide 470;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EH189_1 deposited under accession number ATCC 98290;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 1 to amino acid 53;

(c) fragments of the amino acid sequence of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone EH189_1 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

35. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 20 to nucleotide 541;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 272 to nucleotide 541;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 1 to nucleotide 448;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone EH203_2 deposited under accession number ATCC 98290;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

36. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) the amino acid sequence of SEQ ID NO:18 from amino acid 1 to amino acid 143;

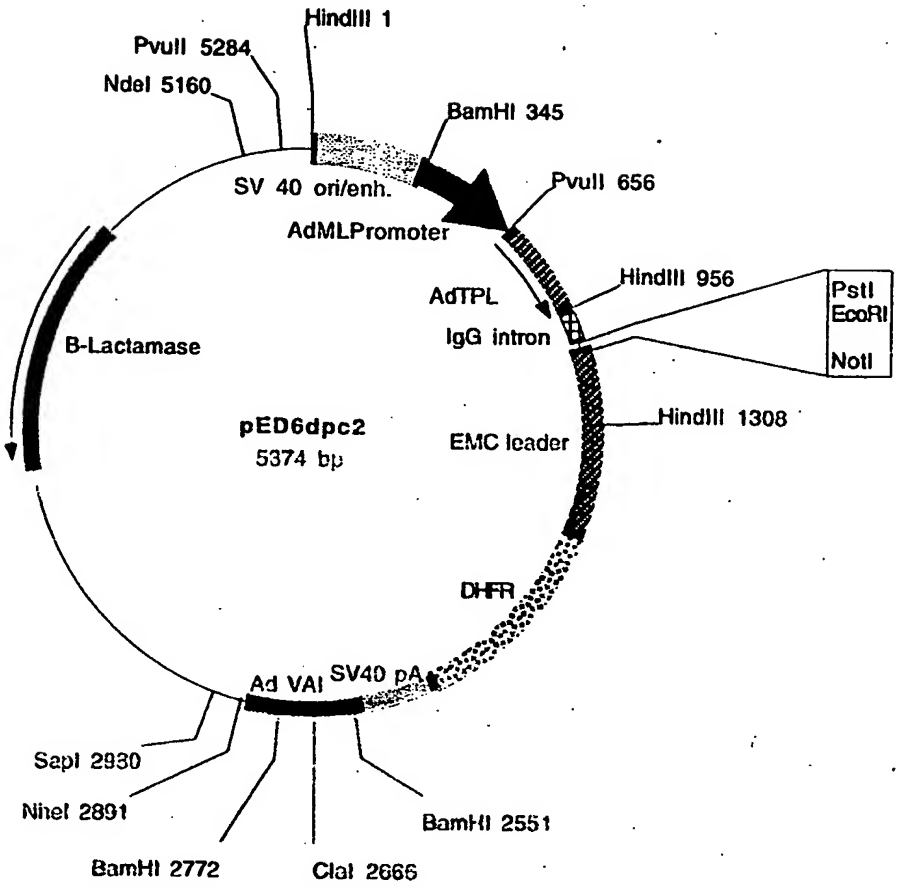
(c) fragments of the amino acid sequence of SEQ ID NO:18; and

(d) the amino acid sequence encoded by the cDNA insert of clone EH203_2 deposited under accession number ATCC 98290;

the protein being substantially free from other mammalian proteins.

37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:17.

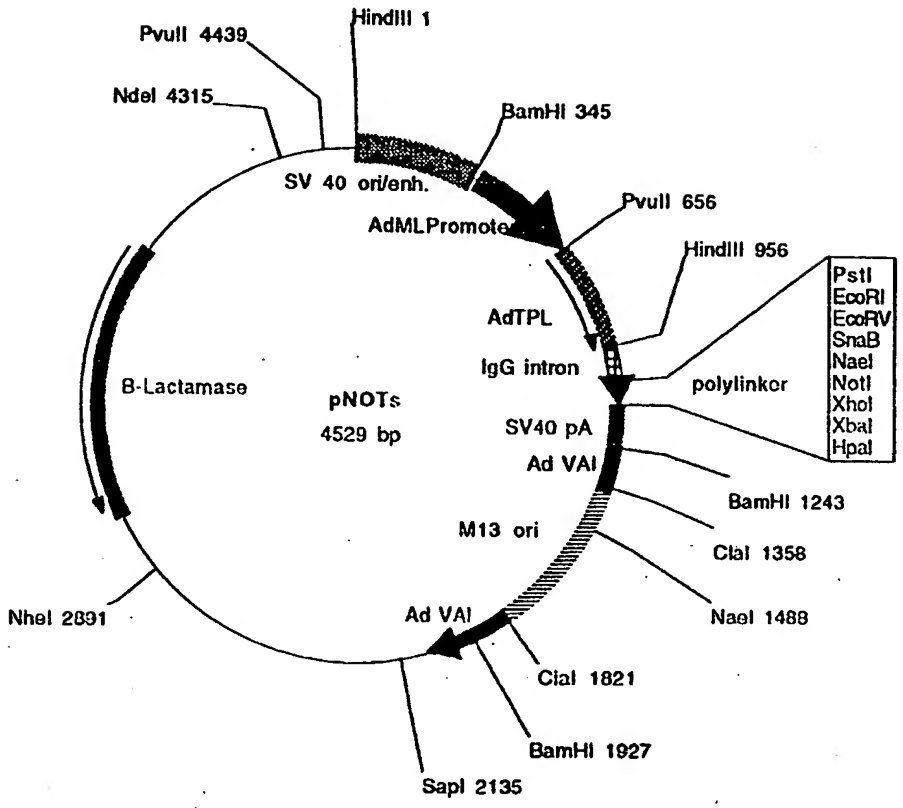
FIGURE 1A



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs
Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI